# Reliance – Analysis of responses to WHO questionnaire – an update

**IPRP**
**Amsterdam, 3 June 2019**

World Health Organization

# Background - a recap

- Reliance a recurring theme from regulatory updates in Kobe, with MC support for focused discussion in Charlotte
- Coincides with ongoing work by WHO and others to promote effective use of resources and access to quality medical products through reliance
- Questionnaire sent to members to gather information on use, challenges, opportunities related to the topic
- WHO requested to summarize responses  to facilitate discussion and possible next steps
- Proposed objective: explore possibility of using IPRP as a forum for promoting reliance

# Feedback

- Detailed responses originally from 8 Members: ANVISA, Brazil; FDA, United States; Health Canada, Canada; HSA, Singapore; MHLW/PMDA, Japan; Swissmedic, Switzerland; TFDA, Chinese Taipei (CT); TGA, Australia.
- Additional responses received from EC/EMA, Europe; CECMED, Cuba; COFEPRIS, Mexico; MEDSAFE, New Zealand; Roszdravnadzor, Russia; TITCK, Turkey.
- Wealth of information and suggestions from a total of 14 respondents, including one regional entity (EU):
  - Clear and consistent messages – reinforced by new inputs
  - Some novel ideas
  - Serves to guide next steps

# Questions

1. *Does your agency practice reliance?*
2. *The WHO has developed definitions for reliance and recognition. Should other terms also be defined?*
3. *Please provide examples of reliance undertaken by your agency or by other agencies to your agency. Describe impact and outcomes.*
4. *Which authorities and institutions serve as a reference for reliance for your agency? Why were they chosen?*
5. *What are the key lessons learned to date in the use of regulatory reliance?*
6. *Why do you practice reliance? Has the use of reliance by your agency had the desired outcome?*
7. *What have been the main challenges and areas for improvement?*
8. *What do you see as the greatest future opportunities for reliance?*
9. *Do you have any further suggestions or comments on the subject of reliance?*

# Definitions

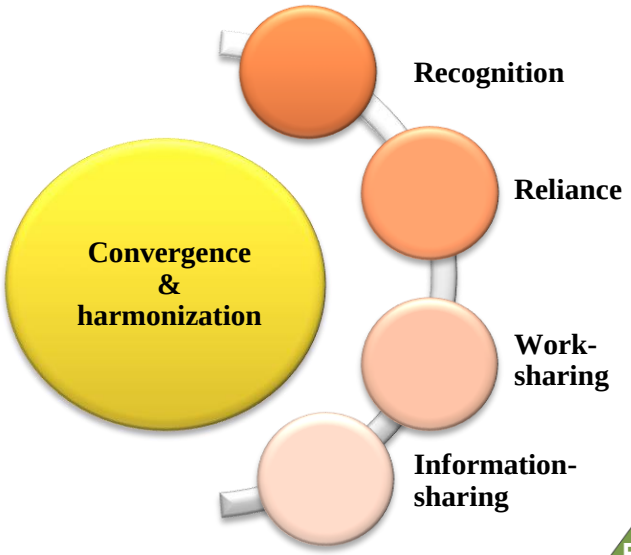
**Reliance:**

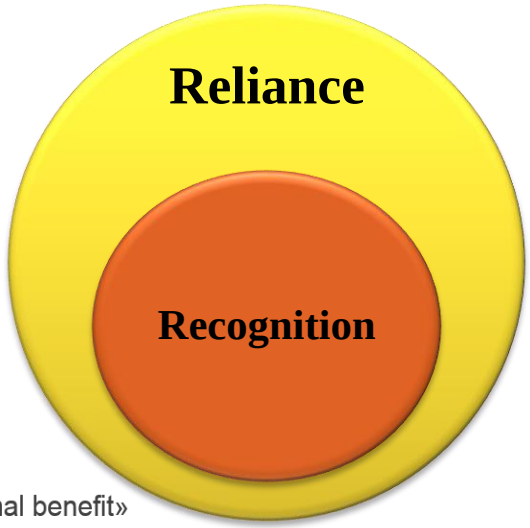
**act whereby a regulatory authority in one jurisdiction may take into account/give significant weight to work performed by another regulator or other trusted institution in reaching its own decision.**

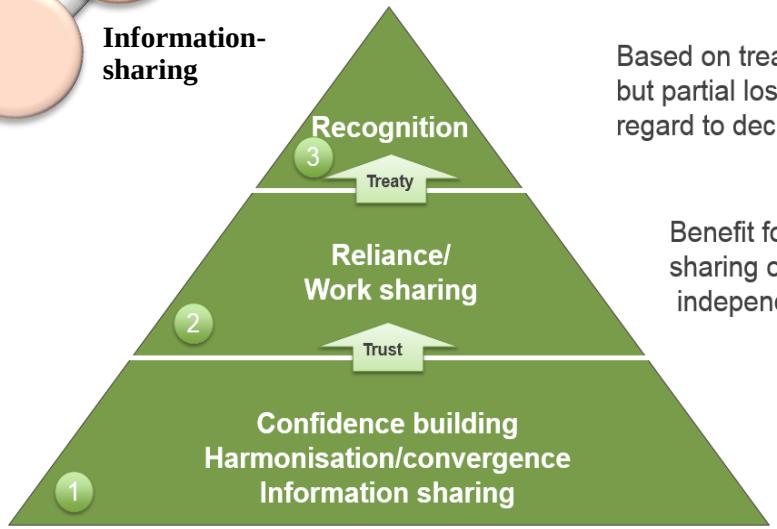
**Recognition:**

**the routine acceptance of the regulatory decision of another regulator or other trusted institution. Recognition indicates that evidence of conformity with the regulatory requirements of country A is sufficient to meet the regulatory requirements of country B.**

# Views on Reliance and Recognition




Based on treaties; «maximal benefit» but partial loss of sovereignty with regard to decision-making

Benefit for regulators; sharing of workload, but independent decisions

«Foundation», Equivalence of requirements



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# Definitions – responses (1)

- Support for additional definitions, including equivalence, facilitated regulatory pathways (FRP) - including simplified/accelerated registration, work-sharing
- Number of terms/definitions currently in use or proposed
- Reliance: only information-sharing or include work-sharing (‘multi-lateral information sharing’)?
- Equivalence: pre-requisite to reliance/recognition; ensure coherence with SPS
- Implicit in various terms used to describe regulatory equivalence/alignment: ‘comparable’, ‘capable’, ‘similar’
- New term to consider: WLA

# Definitions – responses (2)

- Facilitated *regulatory* (*versus registration*) pathways can be applied in broader sense, over product lifecycle; may or may not involve reliance
- Key terms/definitions essential for ensuring common understanding and interpreting guidance
- Common repository – helpful to describe various options/approaches that can favour efficiency of regulatory processes based on scientific evidence and GRP
- Support for WHO to undertake this work – Good Reliance Practices

# Examples (1)

- Variety of pre-requisites, criteria, instruments and schemes
- Examples include (mutual) recognition and work-sharing
- Inspections: GMP, GCP, GLP
- Product assessments:
  - NCEs, biological products, generic drugs,
  - DMFs/ASMFs
  - Components of reviews
  - Complementary medicines/OTCs (planned)
- CTAs (fast track; noncompliance with review target)
- Guidelines

# Examples (2)

- Special circumstances:
  - urgent public health need
  - access to internationally available drugs for unmet medical need (*planned* recognition pathway)
- “In post-market world, more about ‘timeliness’ and ‘accessibility’ of emergent safety information”

# Examples (3)

- Facilitated registration of prequalified products
- New WHO/FDA Pilot on PEPFAR products (HIV)
- Impact of National Regulatory Authorities of Regional Reference (NRArr)
- Equivalence agreements for innovative medicines and devices (Mexico)
- Regulatory Technical Committees for transfer of Technologies (Cuba)
- Turkey: draft legislation on Recognition (Article 38) following self-benchmarking with WHO GBT

# Examples (4) – Regional Examples

- European Union (EU) and Eurasian Economic Union (EAEU) – provides for single markets
- EU: long-established common legal framework for pharmaceuticals, underpinned by common legislation, scientific and regulatory standards, guidelines and procedures (including common application format)
- EAEU: similar arrangements: Treaty and enabling legislation and common databases, allowing for combination of mutual recognition (MA), information-exchange and work-sharing (GMP inspections)
- New Gulf Health Council "centralised" approach
- Ultimate forms of reliance/recognition – possible elsewhere?

# Examples (5)

- Article 58 procedure to promote access to medicines outside EU, taking into account local conditions of use, in collaboration with WHO and experts from target authorities*
- EMA-WHO pilot led to finalization of 'SRA' Collaborative registration Procedure in October 2018
- EU: real-time Information-sharing pilot under IGDRP - decentralized and centralized procedures – as discussed yesterday - lessons learned?

(* NB – similar 'special registration' frameworks in place in a number of other countries, most recently Switzerland)

# Rationale for choice of reference agencies

- Underpinning all responses: principle of establishing that the referenced agency has ‘similar requirements’, robustness or ‘level of control’, or that where differences exist they are known and may be accounted for – i.e. *familiarity and trust*
- Criteria for selection of reference agency:
  - Longstanding ‘reputation‘ in international community
  - Established experience in working with the reference agency and WHO, including bilaterally, internationally
  - Availability of reports and experience gained through use of inspection and assessment reports
  - Direct assessment of requirements and system as part of MRA process; could include joint or observed work
  - Proximity and commonality of products

# Rationale for choice of reference agencies

- Degree of effort undertaken in establishing equivalence also proportional to perceived level of risk (nature of products and area of reliance); may be greater where recognition (of decisions) involved
- Importance of knowing what stands behind/supports regulatory outputs and decisions, including good regulatory and review practices, etc.
- Challenges: time and effort in establishing similarity and differences, including report formats, level of detail (what reported versus what assessed), language, regulations, technical requirements, regulatory practices, standards for employees, etc.

# Perceived benefits (1)

- Common and expected:
  - Regulatory efficiency (faster review, time to approval)
  - More effective use of resources (prioritizing of inspections)
  - Reduced duplication of effort
  - Quality of reviews/inspections/regulatory system
  - Strategy to address resources - insufficient resources to do everything in increasing globalized and complex world
  - Increased regulatory convergence and reduction of country-specific requirements
  - Potential for promoting greater collaboration

# Perceived benefits (2)

- However, responses also reflect aspirations ('potential', 'possible', 'limited experience', 'still early to tell', 'complex', etc.)

***…so are benefits fact or fiction, and how to objectively measure?***

- Observation – probably a mix at this point
- Clear advantages and savings in some cases (for example, reduction in/prioritization of audits/inspections)
- For others, matter of gaining sufficient experience or refinement in approach, taking into account lessons learned
- Nonetheless, support for formalizing and making better use of reliance, in some instances following introduction of necessary enabling legal provisions and policy
- Number of agencies also expressed desire or plans to participate in work-sharing arrangements

# Challenges and considerations (1)

While reliance holds great potential, a number of recurring challenges and considerations were identified:

- Existing differences in regulatory systems (see previous slide) and need for upfront (and continuing) investment to realize benefits
- Access to information, including unredacted assessment reports (particularly challenging for quality information) - promotes understanding of what reviewed and rationale for decisions; also promotes confidence and trust
- Ability to ask questions - PMDA's efforts notable in this regard
- Raises issue of reference agency 'regulatory community responsibility' (next slide)

# Challenges and considerations (2)

Buy-in from all key players, including:

- industry - who must see benefits and downsides and have clear guidance on its application (regulatory pathways defined)
- agency reviewers: need to change mind-set that reliance reduces autonomy, stringency and security – building trust a slow process

Enhanced by a framework for optimizing reliance:

- Review templates, assessor guides that clearly define approach, management support,
- Management and institutional support
- Training and face to face meetings/forum to build trust

# Challenges and considerations (3)

- Importance of having a clearly defined framework within which a particular reliance practice is able to be used
- A clear understanding of the regulatory processes of agencies relied upon, especially how they differ – e.g., evaluator must first understand how pre-market assessment has been conducted
- Legal framework to support reliance extremely helpful, in particular to resolve divergent views
- Importance of building consensus and agreement progressively - critical investment for successful outcomes

# Challenges and considerations (4)

- Successful reliance and cooperation require common approaches to regulatory activities. Many states, especially emerging economies experience need to harmonize regulatory activities, implement quality management systems, adopt standard operating procedures for basic regulatory functions

# Challenges and considerations (5)

- Differences in evidentiary requirements and ‘risk threshold’ for approval (surrogate endpoints, early phase data, risk tolerance)
- Need to maintain scientific capability and competence and clinical judgement in decision-making and labelling, bridging decisions in other countries to local benefit-harm context
- Related to the above, the consequences of reference agencies increasingly relying on other reference agencies and organizational efforts to understand and develop areas of expertise
- Implications of adaptive licensing/early approvals and challenges posed to other agencies who may wish to leverage

# Challenges and considerations (6)

- Secure platform and procedures for the exchange and management of non-public information
- Differences in products and production sites, sponsors/legal manufacturers
- Confidence in reliability of review reports provided by applicants
- Metrics: how to measure and document success? Outcome difficult to measure objectively (however uptake of reliance pathways suggestive of impact)

# Challenges and considerations (7)

- Reliance not an opportunity to reduce resources of participating NRAs, but rather ensure agencies avoid duplication and focus resources on key activities that bring value to the populations they serve
- Particularly useful for small market/small regulator to ensure we make the most out of limits resources, achieving the best outcomes, while retaining a high degree of regulatory stringency

# Opportunities (1)

- Harmonize structure and format of inspection reports and include more discrete data fields/structured-format content to better leverage foreign inspections
- Similarly, provide product assessment reports in searchable electronic format
- Opportunity to consider convergence/harmonization of regulatory formats and guides to better leverage one another's reports? NB - ACSS and IPRP Quality WG have also undertaken work in this area
- Potential for further MRAs (inspection) – build on work done by ICMRA with PIC/S
- International workshop on reliance: experiences/best practices

# Opportunities (2)

- Added emphasis on post-approval phase:
  - Proactive sharing of post-market safety data
  - Establish standards for timeliness and minimum information content for posting emergent safety issues or regulatory actions
  - Standardization of Good Vigilance Practices, including roles and responsibilities of industry in collecting foreign safety data
  - Support by reference agencies in relation to early approvals and post-market safety issues
  - Reliance/work-sharing in the area of PV, post-authorisation safety and efficacy monitoring

# Opportunities (3)

- Discussions regarding how reference agencies provide assessment reports, for example:
  - Unredacted reports shared with sponsor?
  - Information available on website?
  - Policy and procedures for sharing with other regulators?
  - Ability to interact with reference agencies?
- Broadening of existing reliance frameworks to include other therapeutic/health products and new technologies
- Substantial variations
- Wider acceptance and application of reliance and work-sharing worldwide: ***move from pilot stages to 'daily business'***

# Opportunities (4)

- Important to ensure that the definitions of reliance wide enough to include regional regulatory systems such as that in the EU, but also those being developed in Africa, Caribbean, Gulf Council, Latin and South America, etc.
- (In addition to benchmarking) DRAs of ICH countries may create fora for emerging economies where the latter may become more familiar with advanced regulatory practices, approaches to assessment of new types of medicines which will contribute to wider use of reliance
- Opening of ICH…favours convergence
- Within the Americas: project on better use of CPP and PAHO project on regulatory convergence

# Opportunities (5) – GBT and WLA

Assessment of NRAs with the Global Benchmarking Tool (GBT) of WHO/PAHO and the WHO-listed authorities' (WLAs) will provide evidences of NRA's performance and enable trust in decisions of NRAs….

….. active decision to 'regulate through reliance' is a positive attribute and not something that penalises or downgrades an authority being assessed…..

……WHO efforts on capacity building/maturity assessment became  important tool for promotion of good regulatory practices and qualification of DRAs, helping to adjust national performance to common standards and thus 'increase the room for reliance and recognition'

# Observations

- Growing body of examples and experience, however, potential of reliance won't be achieved unless challenges addressed
- Could be on the verge of something transformative - regulatory community ready?
- Timing right: work of WHO/PAHO; regulators, others
- Role for IPRP as a forum to discuss ideas?
- Build on Information sharing for generics? Extend to innovative products?
- Still need to capture experiences of more countries
- Growing recognition of importance/value of benchmarking

"If you want to rely on something, trust is needed. It might be interesting to elaborate on what is needed to build trust and establish confidence. How should a successful cooperation look? Could there be a 'Best Practice Guide for trusted cooperation'? ( - WHO preparing a Good Reliance Practices)"

# Possible next steps

- IPRP serve as a forum to provided input/feedback to WHO in development of good reliance practices guide and implementation tool kit as well as WLA framework
- Explore some of the ideas suggested by IPRP members
- Contribute to a repository on reliance and collaboration
- Article on reliance based on IPRP member responses

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# Thank you!